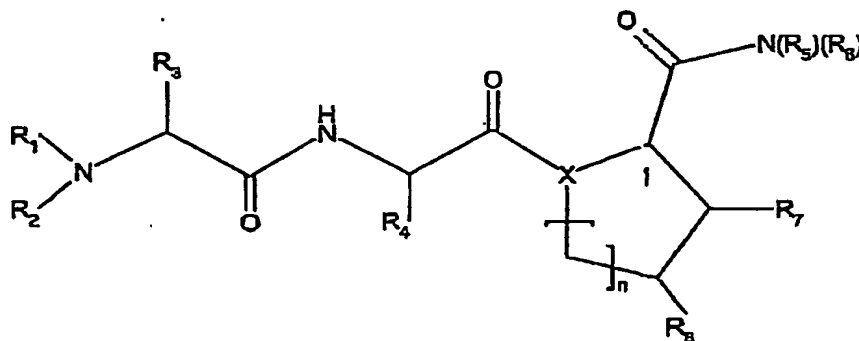


ART 34 AMST

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We claim:

1. A compound of the formula (I)



wherein

R₁ is H;

R₂ is H, C₁-C₄alkyl which is unsubstituted or substituted by one or more substituents selected from halogen, -OH, -SH, -OCH₃, -SCH₃, -CN, -SCN and nitro;

R₃ is H, -CF₃, -C₂F₅, -CH₂Z or R₂ and R₃ together form with the nitrogen form a C₃-C₆heteroaliphatic ring;

Z is H, -OH, F, Cl, -CH₃, -CF₃, -CH₂Cl, -CH₂F or -CH₂OH;

R₄ is C₁-C₁₆ straight chain alkyl, C₃-C₁₀ branched chain alkyl, -(CH₂)₀₋₆-C₃-C₇-cycloalkyl, -(CH₂)₁₋₆-Z₁, -(CH₂)₀₋₆-phenyl, and -(CH₂)₀₋₆-het, wherein the alkyl, cycloalkyl and phenyl substituents are unsubstituted or substituted;

Z₁ is -N(R₉)-C(O)-C₁-C₁₀alkyl, -N(R₉)-C(O)-(CH₂)₁₋₆-C₃-C₇-cycloalkyl, -N(R₉)-C(O)-(CH₂)₀₋₆-phenyl, -N(R₉)-C(O)-(CH₂)₁₋₆-het, -C(O)-N(R₁₀)(R₁₁), -C(O)-O-C₁-C₁₀alkyl, -C(O)-O-(CH₂)₁₋₆-C₃-C₇-cycloalkyl, -C(O)-O-(CH₂)₀₋₆-phenyl, -C(O)-O-(CH₂)₁₋₆-het, -O-C(O)-C₁-C₁₀alkyl, -O-C(O)-(CH₂)₁₋₆-C₃-C₇-cycloalkyl, -O-C(O)-(CH₂)₀₋₆-phenyl, -O-C(O)-(CH₂)₁₋₆-het, wherein the alkyl, cycloalkyl and phenyl substituents are unsubstituted or substituted;

het is a 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O and S, or an 8-12 membered fused ring system including at least one 5-7 membered heterocyclic ring containing 1, 2 or 3 heteroatoms selected from N, O, and S, which heterocyclic ring or fused ring system is unsubstituted or substituted on a carbon atom by halogen, hydroxy, C₁-C₄alkyl, C₁-C₄alkoxy, nitro, -O-C(O)-C₁-C₄alkyl or -C(O)-O-C₁-C₄alkyl or on a nitrogen by C₁-C₄alkyl, -O-C(O)-C₁-C₄alkyl or -C(O)-O-C₁-C₄alkyl;

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ART 34 AND 1

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R_9 is H, $-\text{CH}_3$, $-\text{CF}_3$, $-\text{CH}_2\text{OH}$ or CH_2Cl ;

R_{10} and R_{11} are each independently H, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-(\text{CH}_2)_{1-6}\text{-C}_3\text{-C}_7$ cycloalkyl, $-(\text{CH}_2)_{0-6}$ phenyl, wherein the alkyl, cycloalkyl and phenyl substituents are unsubstituted or substituted, or R_{10} and R_{11} together with the nitrogen are het;

X is CH or N;

R_5 is H, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-(\text{CH}_2)_{1-6}\text{-C}_3\text{-C}_7$ cycloalkyl, $-\text{C}_1\text{-C}_{10}$ alkyl-aryl, $-(\text{CH}_2)_{0-6}\text{-C}_3\text{-C}_7$ cycloalkyl- $(\text{CH}_2)_{0-6}$ phenyl, $-(\text{CH}_2)_{0-4}\text{CH-}((\text{CH}_2)_{1-4}\text{phenyl})_2$, $-(\text{CH}_2)_{0-6}\text{CH(phenyl)}_2$, $-\text{C(O)-C}_1\text{-C}_{10}$ alkyl, $-\text{C(O)-}(\text{CH}_2)_{1-6}\text{-C}_3\text{-C}_7$ cycloalkyl, $-\text{C(O)-}(\text{CH}_2)_{0-6}$ phenyl, $-(\text{CH}_2)_{1-6}\text{-het}$, $-\text{C(O)-}(\text{CH}_2)_{1-6}\text{-het}$, wherein the alkyl, cycloalkyl, phenyl and aryl substituents are unsubstituted or substituted;

R_6 is H, methyl, ethyl, $-\text{CF}_3$, $-\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{Cl}$; or

R_5 and R_6 together with the nitrogen are het;

R_7 and R_8 are cis relative to the acyl substituent at the one position of the ring and are each independently H, $-\text{C}_1\text{-C}_{10}$ alkyl, $-\text{OH}$, $-\text{O-C}_1\text{-C}_{10}$ alkyl, $-(\text{CH}_2)_{0-6}\text{-C}_3\text{-C}_7$ cycloalkyl, $-\text{O-}(\text{CH}_2)_{0-6}$ aryl, phenyl, $-(\text{CH}_2)_{1-6}\text{-het}$, $-\text{O-}(\text{CH}_2)_{1-6}\text{-het}$, $-\text{N(R}_{12}\text{)(R}_{13})$, $-\text{S-R}_{12}$, $-\text{S(O)-R}_{12}$, $-\text{S(O)}_2\text{-R}_{12}$, $-\text{S(O)}_2\text{-NR}_{12}\text{R}_{13}$ wherein the alkyl, cycloalkyl and aryl substituents are unsubstituted or substituted;

R_{12} and R_{13} are independently H, $\text{C}_1\text{-C}_{10}$ alkyl, $-(\text{CH}_2)_{0-6}\text{-C}_3\text{-C}_7$ cycloalkyl, $-(\text{CH}_2)_{0-6}\text{-(CH)}_0$, $-(\text{CH}_2)_{0-6}\text{-(CH)}_1$, $-(\text{CH}_2)_{0-6}\text{-(CH)}_2$, $-\text{C(O)-C}_1\text{-C}_{10}$ alkyl, $-\text{C(O)-}(\text{CH}_2)_{1-6}\text{-C}_3\text{-C}_7$ cycloalkyl, $-\text{C(O)-O-}(\text{CH}_2)_{0-6}$ aryl, $-\text{C(O)-}(\text{CH}_2)_{0-6}\text{-O-fluorenyl}$, $-\text{C(O)-NH-}(\text{CH}_2)_{0-6}$ aryl, $-\text{C(O)-}(\text{CH}_2)_{0-6}$ aryl, $-\text{C(O)-}(\text{CH}_2)_{1-6}\text{-het}$, wherein the alkyl, cycloalkyl and aryl substituents are unsubstituted or substituted; or a substituent that facilitates transport of the molecule across a cell membrane, or R_{12} and R_{13} together with the nitrogen are het;

aryl is phenyl or naphthyl which is unsubstituted or substituted;

n is 0, 1 or 2;

and wherein

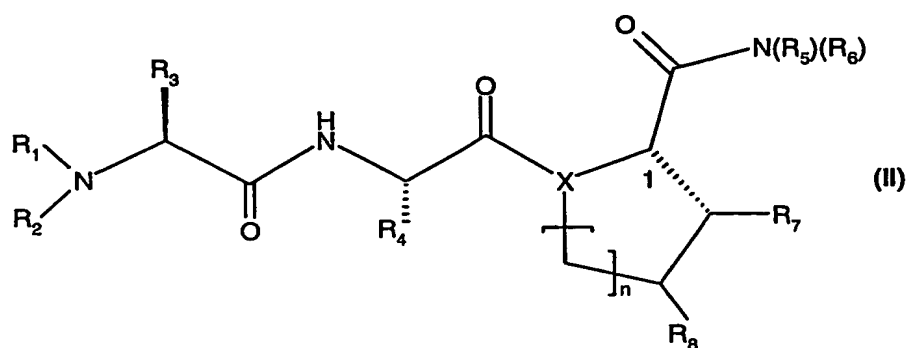
substituted alkyl substituents are substituted by one or more substituents selected from a double bond, halogen, OH, $-\text{O-C}_1\text{-C}_8$ alkyl, $-\text{S-C}_1\text{-C}_8$ alkyl and $-\text{CF}_3$;

substituted cycloalkyl substituents are substituted by one or more substituents selected from a double bond, $\text{C}_1\text{-C}_8$ alkyl, halogen, OH, $-\text{O-C}_1\text{-C}_8$ alkyl, $-\text{S-C}_1\text{-C}_8$ alkyl and $-\text{CF}_3$; and

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substituted phenyl or aryl are substituted by one or more substituents selected from halogen, hydroxy, C₁-C₄ alkyl, C₁-C₄ alkoxy, nitro, -CN, -O-C(O)-C₁-C₄alkyl and -C(O)-O-C₁-C₄-alkyl, or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein R₂ is H or methyl and R₃ is methyl.
3. A compound of claim 1 wherein n is 1.
4. A compound of claim 1 having the stereochemistry indicated in formula II



5. A compound of claim 4 wherein R₂ is H or methyl and R₃ is methyl.
6. A compound of claim 4 wherein n is 1.
7. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula I according to claim 1.
8. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula II according to claim 4.
9. A pharmaceutical composition according to claim 7 for treating a proliferative disease.
10. A pharmaceutical composition according to claim 8 for treating a proliferative disease.

11. A method of treating a proliferative disease which comprises administering a therapeutically effective amount of a compound of formula I according to claim 1 to a mammal in need of such treatment.

10. A method of treating a proliferative disease which comprises administering a therapeutically effective amount of a compound of formula II according to claim 4 to a mammal in need of such treatment.

11. A method of claim 11 wherein the mammal is a human.

12. A method of claim 12 wherein the mammal is a human.

13. Use of a compound of formula I according to claim 1 for the manufacture of a medicament for treating a proliferative disease.

14. Use of a compound of formula II according to claim 4 for the manufacture of a medicament for treating a proliferative disease.